Пара- и эндокринная сигнализация

с/к «Межклеточная коммуникация»
Лекция 5

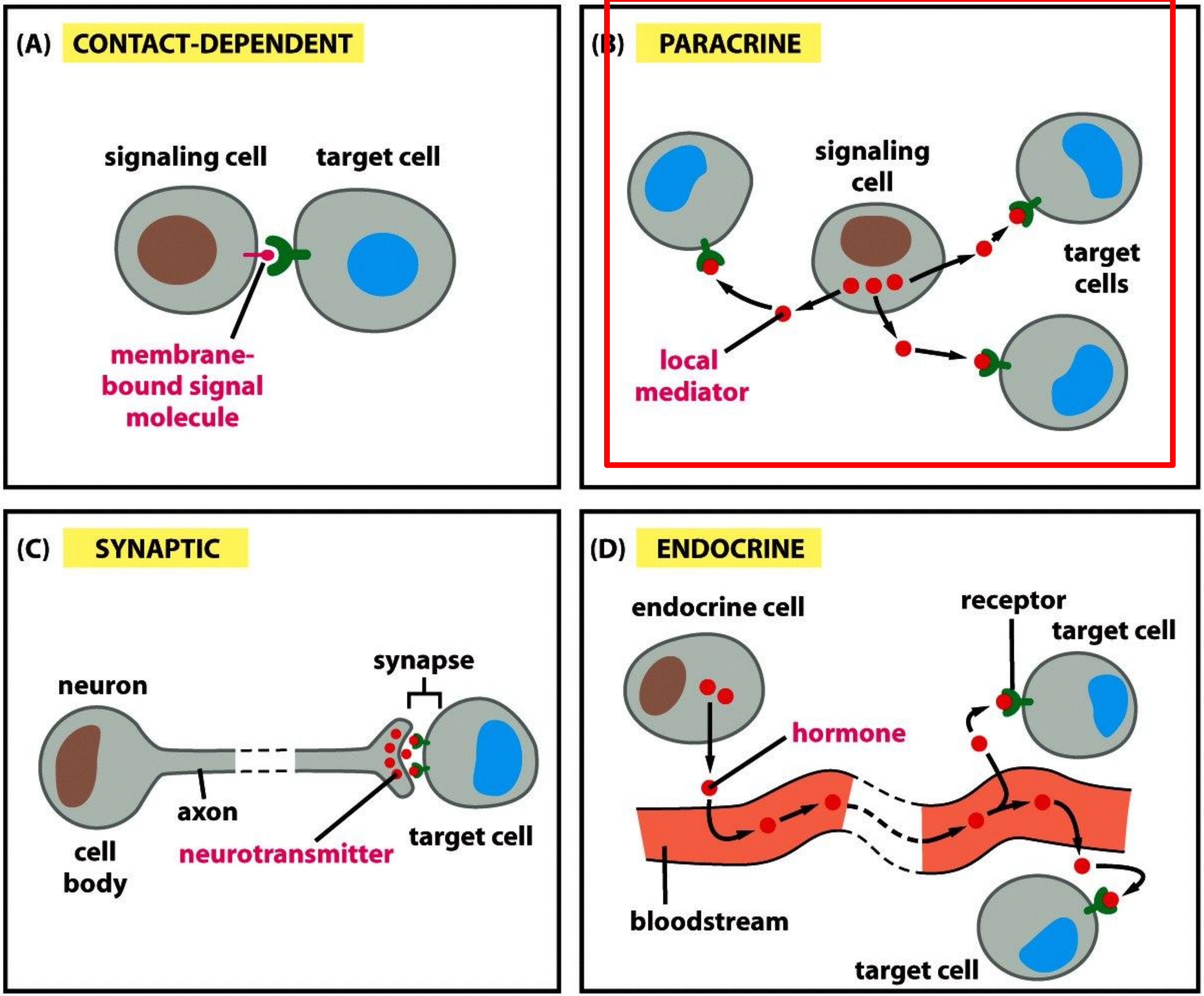
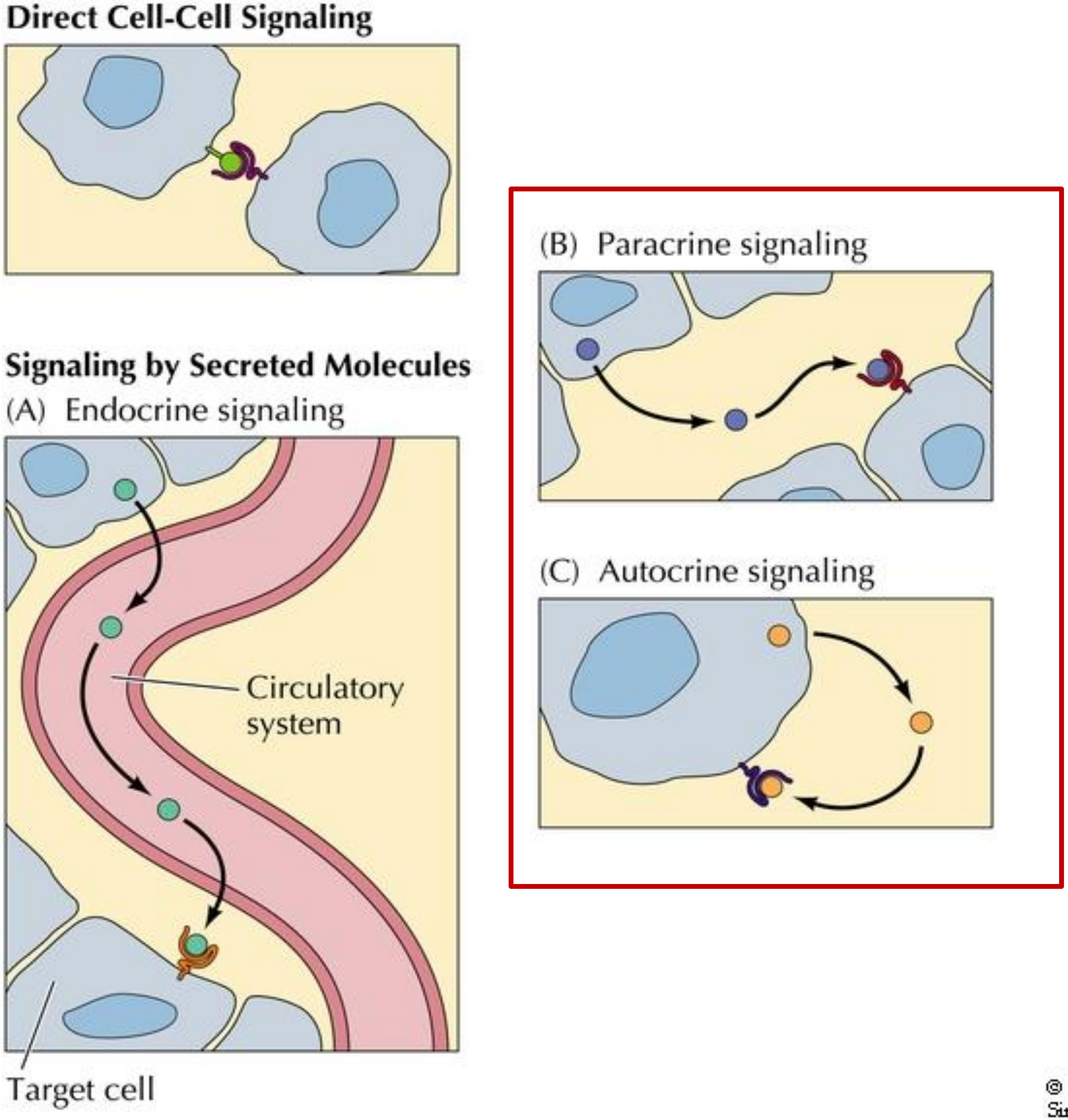


Figure 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)



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Cytokines, Hormones, and Growth Factors

1. All three are secreted soluble factors that elicit their biological effects at pM concentrations.
2. Growth factors tend to be produced constitutively, whereas cytokine production is carefully regulated. Cytokines are usually secreted after activation of a particular cell, and secretion is short-lived, generally ranging from a few hours to a few days.
3. Hormones generally act long range in an endocrine fashion, most cytokines act over a short distance in an autocrine or paracrine fashion.
4. Most hormones are produced by specialized glands and tend to have a unique action on one or a few types of target cell. In contrast, cytokines are often produced by a variety of cells and bind to receptors present on numerous types of cells.

Paracrine Regulators

Prostaglandins

- A diverse group of fatty acids that are produced in almost every organ
- Regulate a variety of functions
- Synthesis is inhibited by **nonsteroidal anti-inflammatory drugs (NSAIDs)** such as aspirin and ibuprofen

The endothelium is a rich source of paracrine regulators

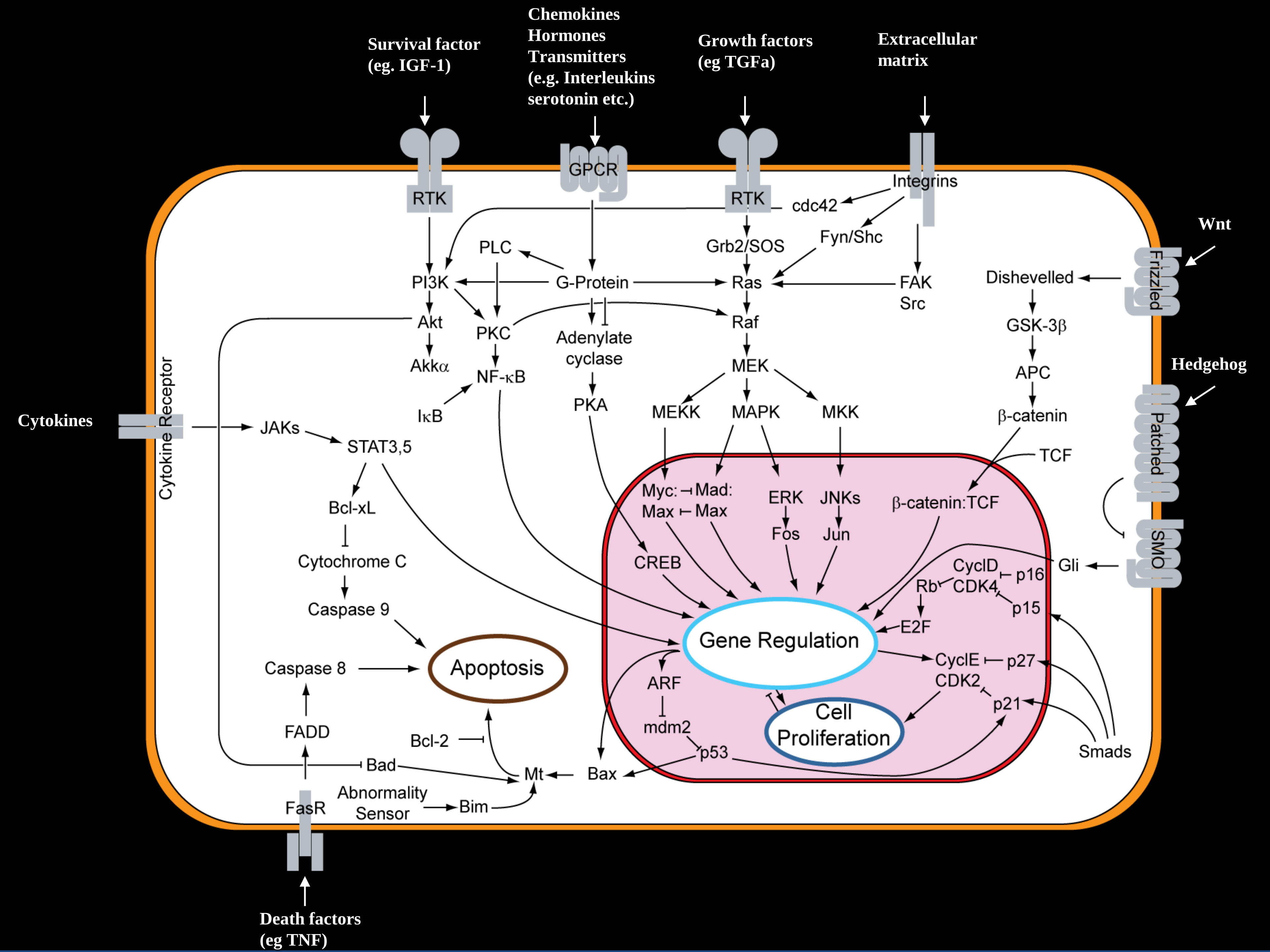
- **Nitric oxide (NO)** which promotes vasodilation
- **Endothelin** which stimulates vasoconstriction
- **Bradykinin** which promotes vasodilation

Growth factors are proteins that promote growth and cell division in specific organs

  - **Epidermal growth factor** = Skin
  - **Nerve growth factor** = Neurons
  - **Insulin-like growth factor** = Bone
  - **Cytokines** = Immune system

Secreted Signaling Molecules

- FGF Family
- Hedgehog Family
- Wnt Family
- TGFβ Superfamily
  - TGFβ Family
  - Activin Family
  - BMP Family
- EGF Family
- PDGF Family
- Retinoids
- HGF/Scatter Factor
- Neurotrophins
- Semaphorins
- Cytokines



Survival factor
(eg. IGF-1)

Chemokines
Hormones
Transmitters
(e.g. Interleukins
serotonin etc.)

Growth factors
(eg TGFa)

Extracellular
matrix

Wnt

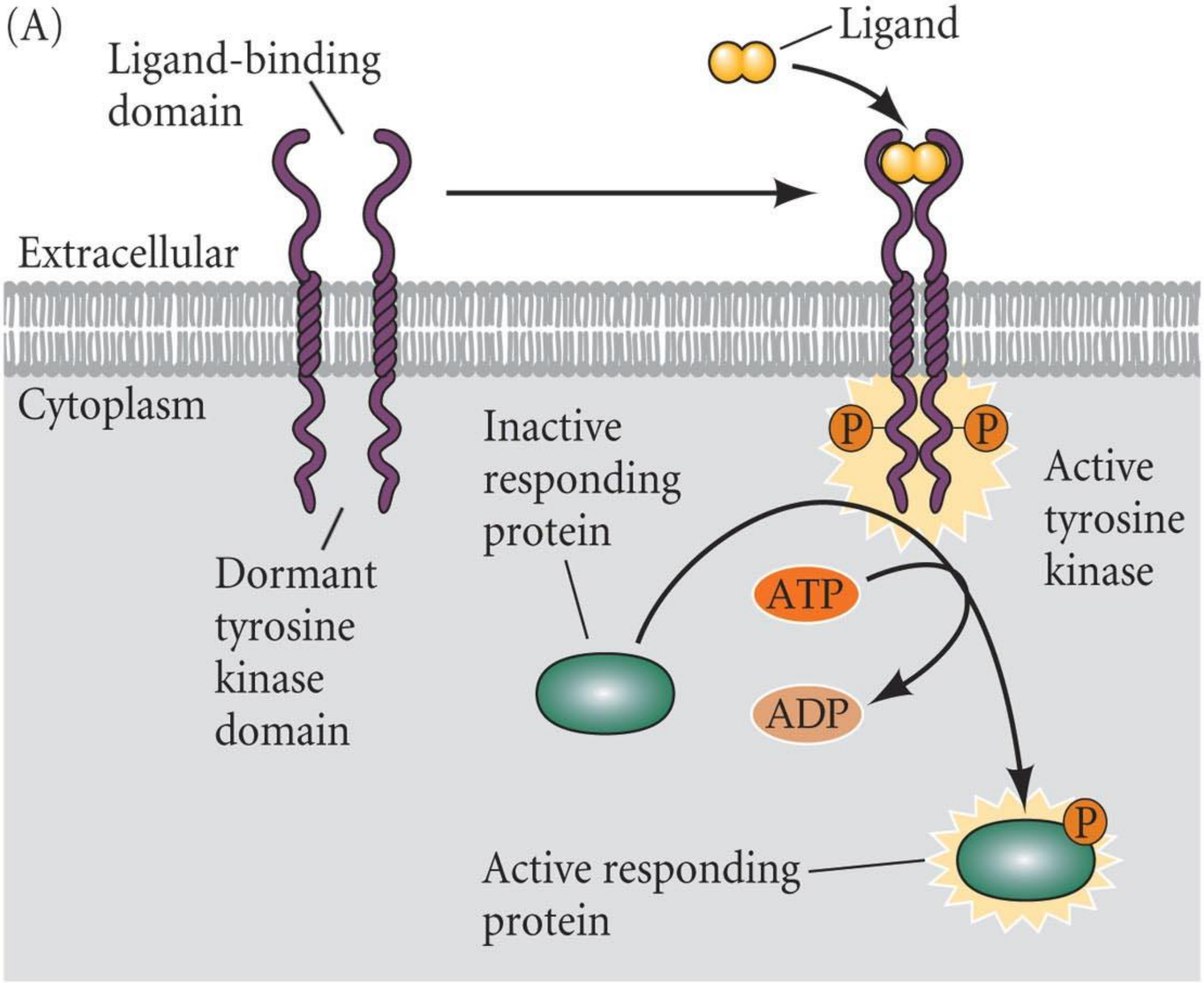
Hedgehog

Cytokines

Death factors
(eg TNF)

RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Frizzled
Dishevelled
Akt
PKC
Adenylate cyclase
Raf
GSK-3β
Akkα
NF-κB
MEK
APC
IκB
PKA
MEKK
MAPK
MKK
β-catenin
Patched
Cytokine Receptor
JAKs
STAT3,5
TCF
Myc: Max
Mad: Max
ERK
JNKs
β-catenin:TCF
Fos
Jun
SMO
Bcl-xL
CREB
Gli
CyclD
CDK4
p16
Rb
p15
Cytochrome C
E2F
Caspase 9
Gene Regulation
Caspase 8
Apoptosis
CyclE
CDK2
p27
ARF
Cell Proliferation
p21
FADD
Bcl-2
mdm2
Bad
p53
Smads
Mt
Bax
FasR
Abnormality Sensor
Bim

Paracrine Factors action



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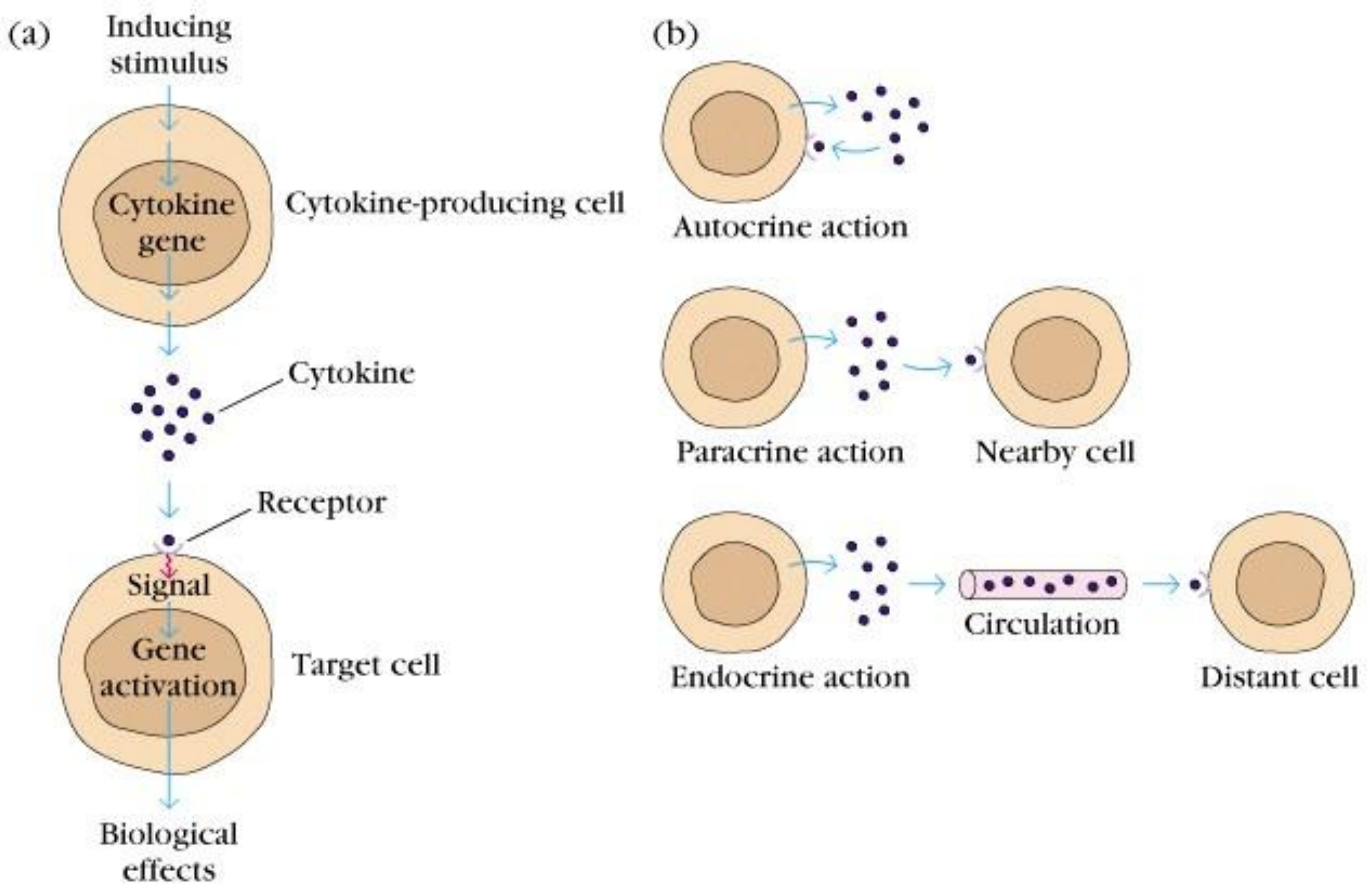
Cytokines, like hormones, can act in autocrine, paracrine, or endocrine fashion



Cytokine nomenclature

- **Lymfokines** - produced by activated **T lymphocytes** direct the immune system response by signaling between its cells

- **Interleukins** - presumed targets are principally **leukocytes**.

- **Chemokines** - specific class of cytokines. Mediates chemoattraction (**chemotaxis**) between cells, stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.

- **Monokines** - derived primarily from mononuclear cells such as **macrophages**.

Cytokines: main functions

- **Hematopoiesis** (ex. CSFs, colony stimulating factors).
- **Inflammatory reaction** (ex. IL1, TNF).
- **Chemotaxis** (ex. IL8, MIP1- macrophage inflammatory protein 1, BLC – B-lymphocyte chemoatractant).
- **Immunostimulation** (ex. IL12, IFNγ).
- **Suppression** (ex. IL10).
- **Angiogenesis** (ex. VEGFs - vacsular endothelial growth factor).
- **Embryogenesis** (ex. TGF-β, LT - lymphotoxin).

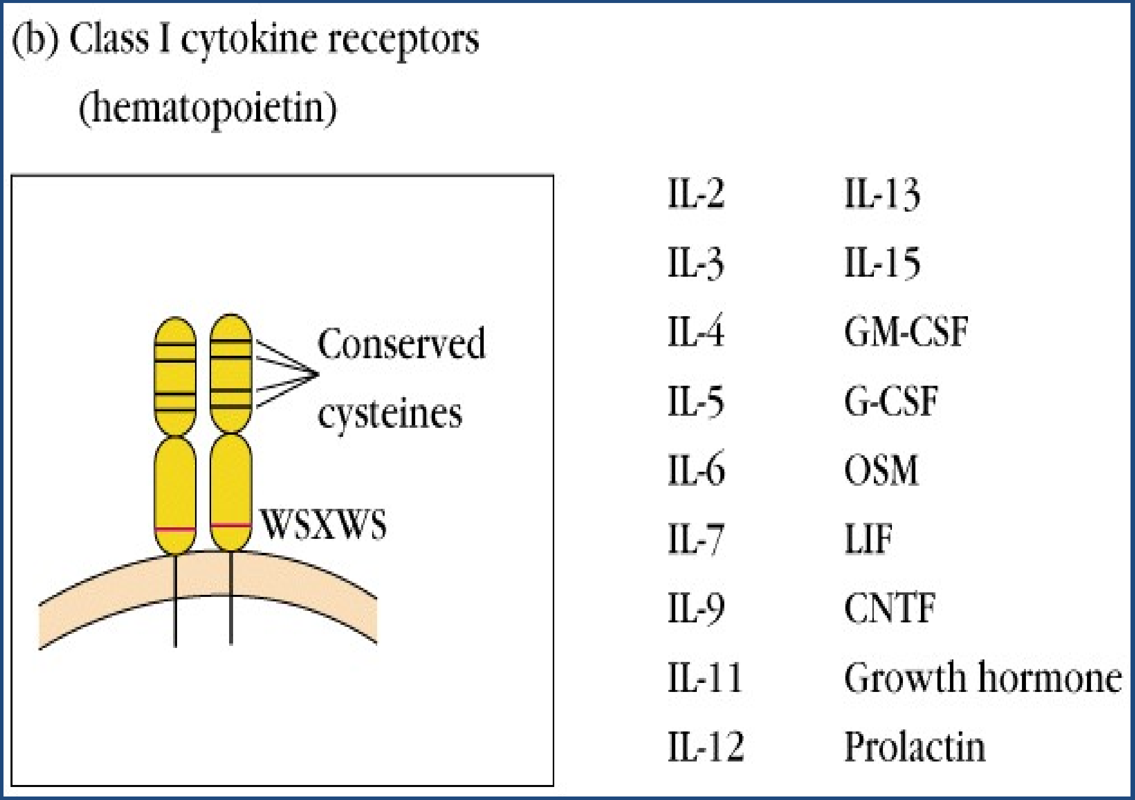
Classification

❑ Type I cytokine receptor or hematopoietin receptor family : IL 2, IL 3, IL 4, IL 5, IL 6, IL7, IL 9, IL 13, IL 15, GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) and G-CSF (Granulocyte-Colony Stimulation Factor)

❑ Type II cytokine receptors or interferon receptors

❑ Transforming growth factor receptor
❑ Tumor necrosis factor receptor
❑ Immunoglobulin superfamily (IgSF)
❑ Chemokine receptors (seven transmembrane helix)

Type I cytokine receptor

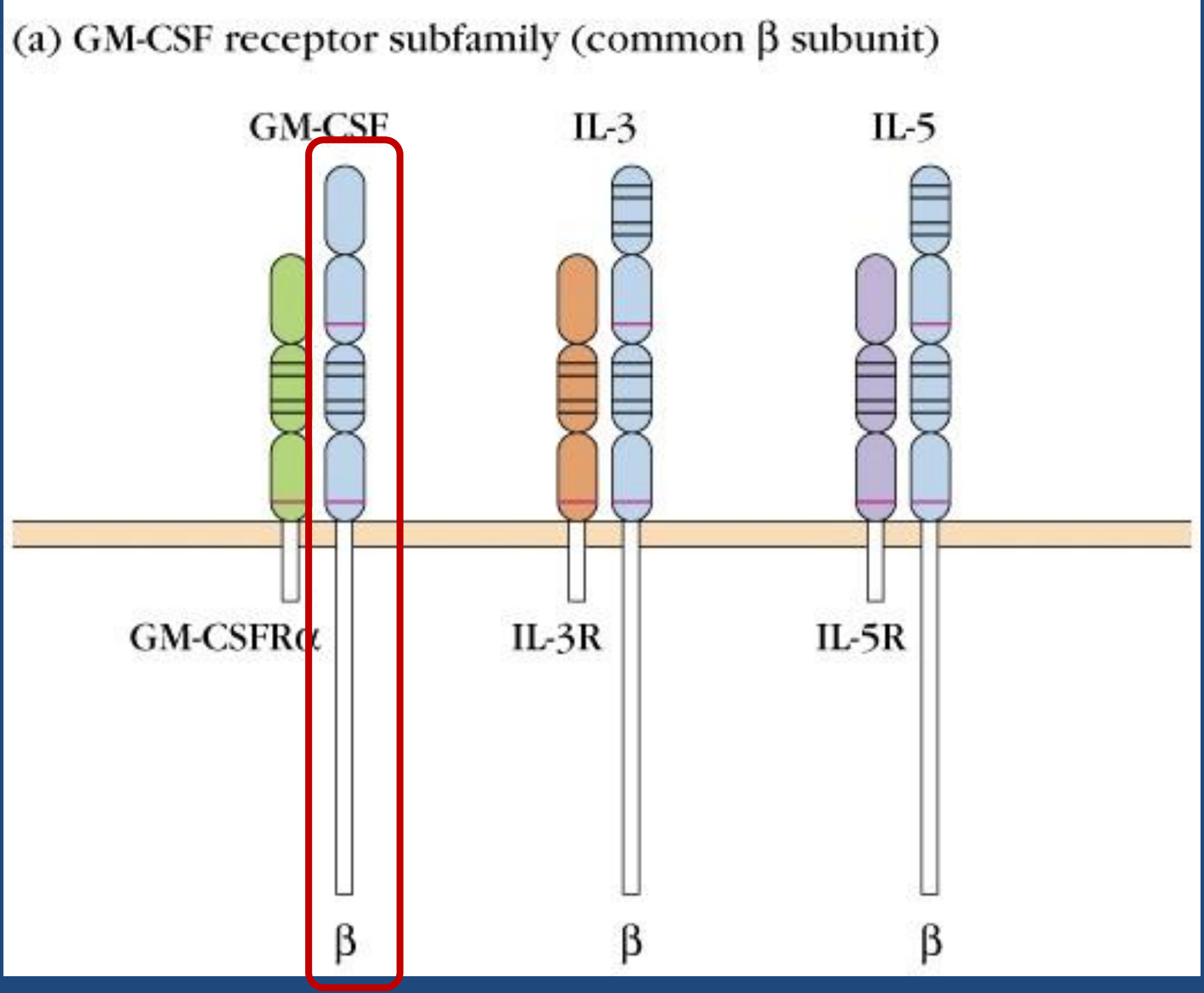


(b) Class I cytokine receptors
(hematopoietin)

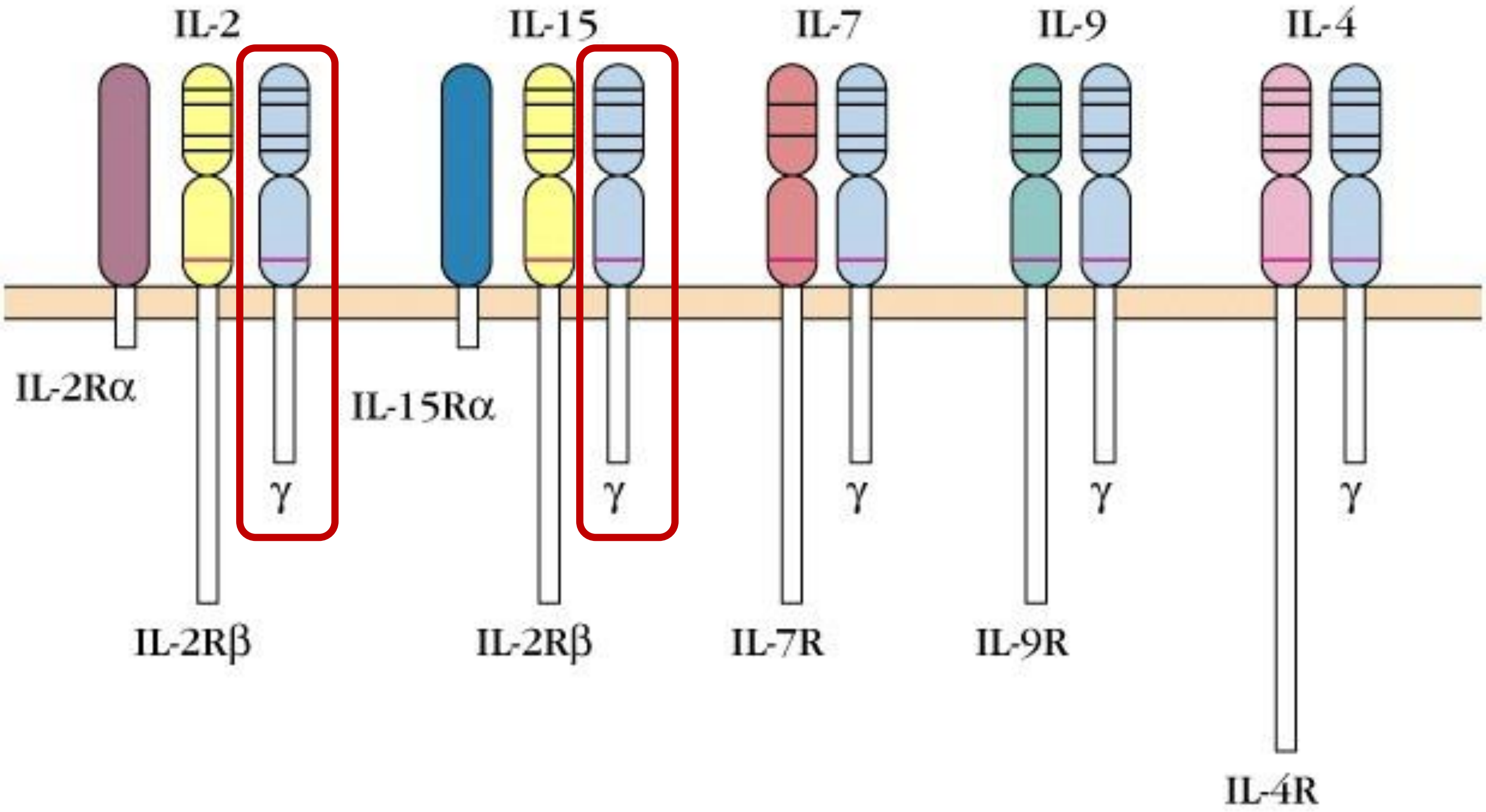
- IL-2
- IL-3
- IL-4
- IL-5
- IL-6
- IL-7
- IL-9
- IL-11
- IL-12
- IL-13
- IL-15
- GM-CSF
- G-CSF
- OSM
- LIF
- CNTF
- Growth hormone
- Prolactin

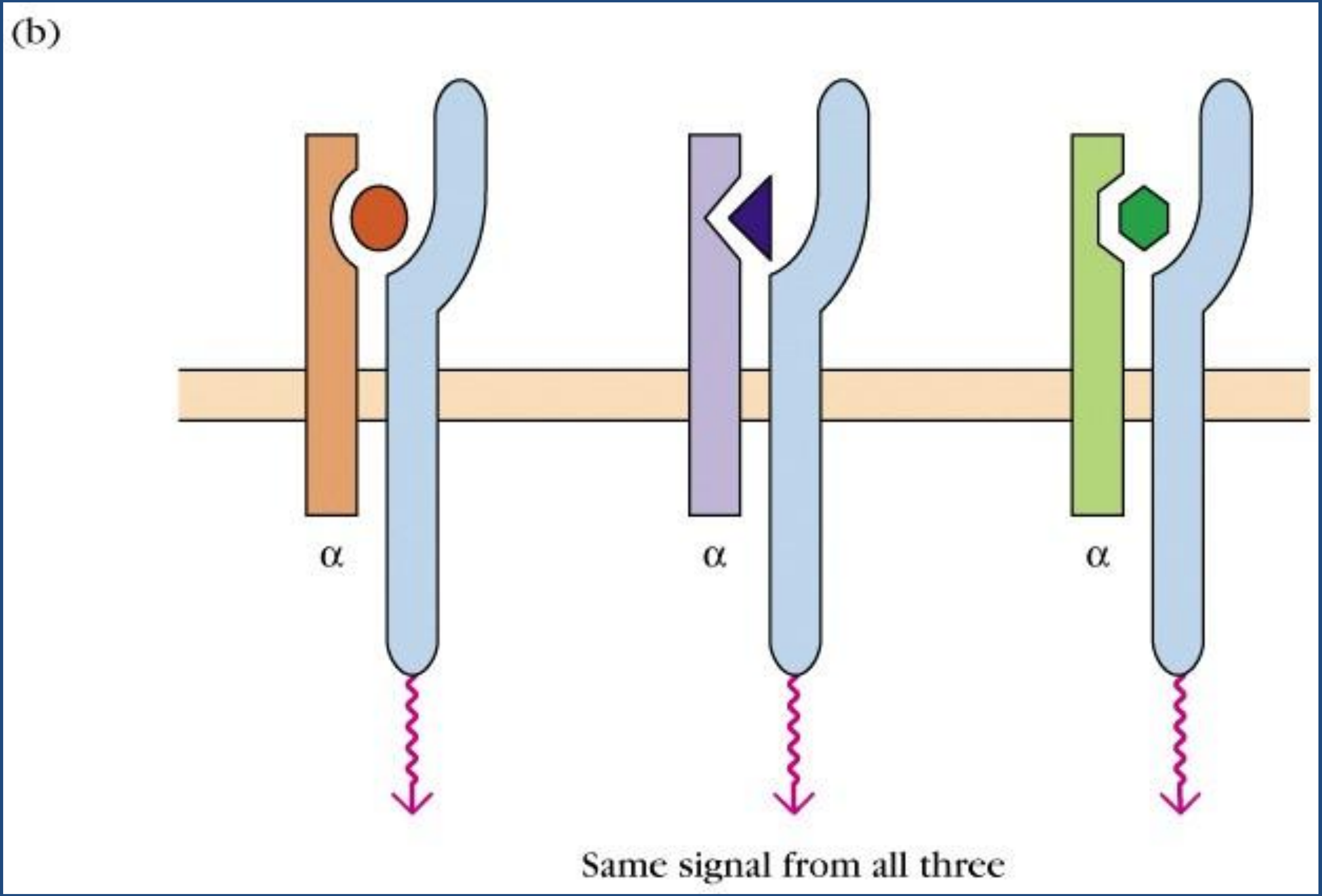
These receptors are also known under the name **hematopoetin receptors**, and share a Trp-Ser-X-Ser-Trp motif (WSXWS) in the extracellular portion adjacent to the cell membrane.

3 Subfamilies of Class I Cytokine Receptors



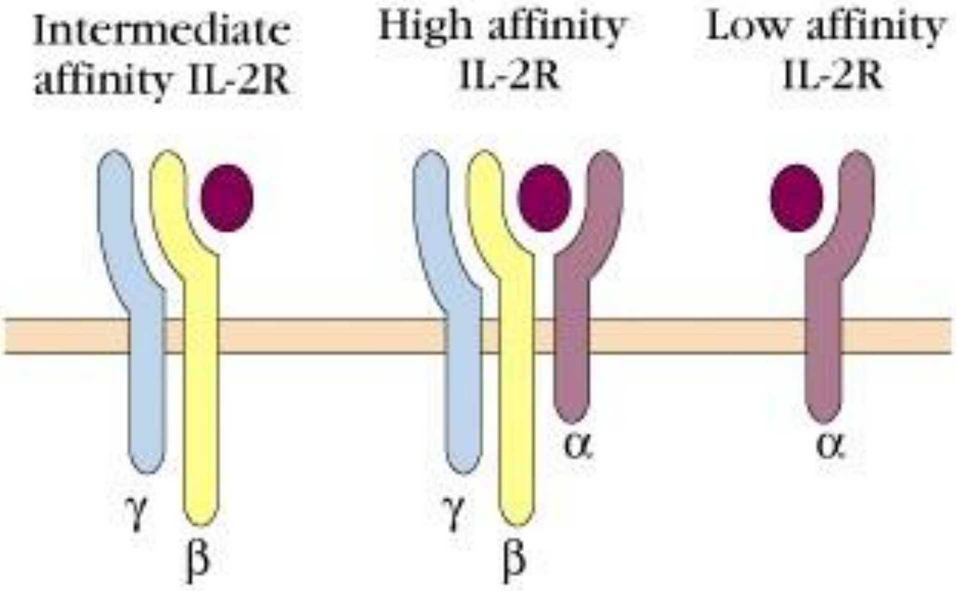
(c) IL-2 receptor subfamily (common γ subunit)





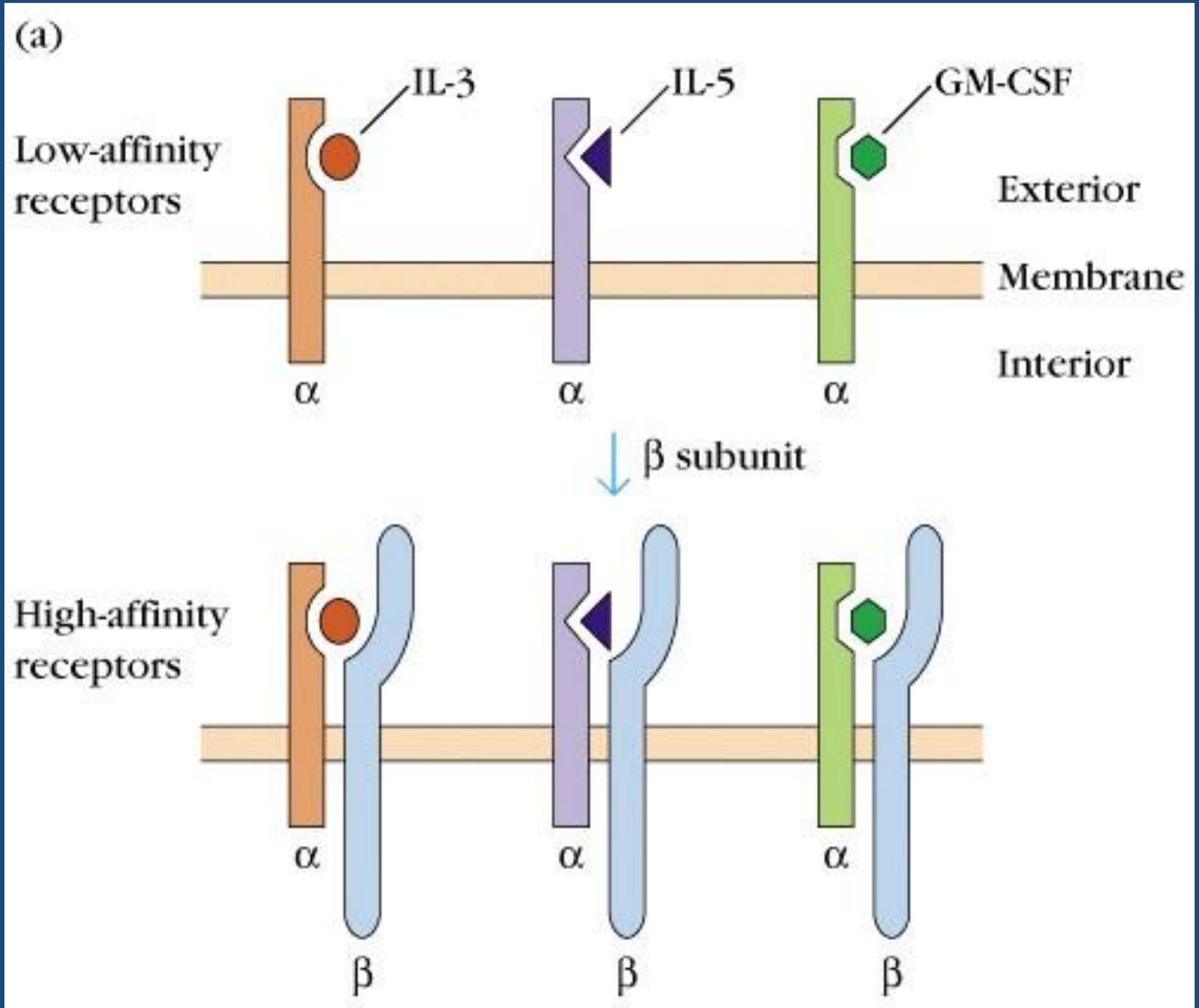
Same signal from all three

3 Forms of the IL-2 Receptor by affinity

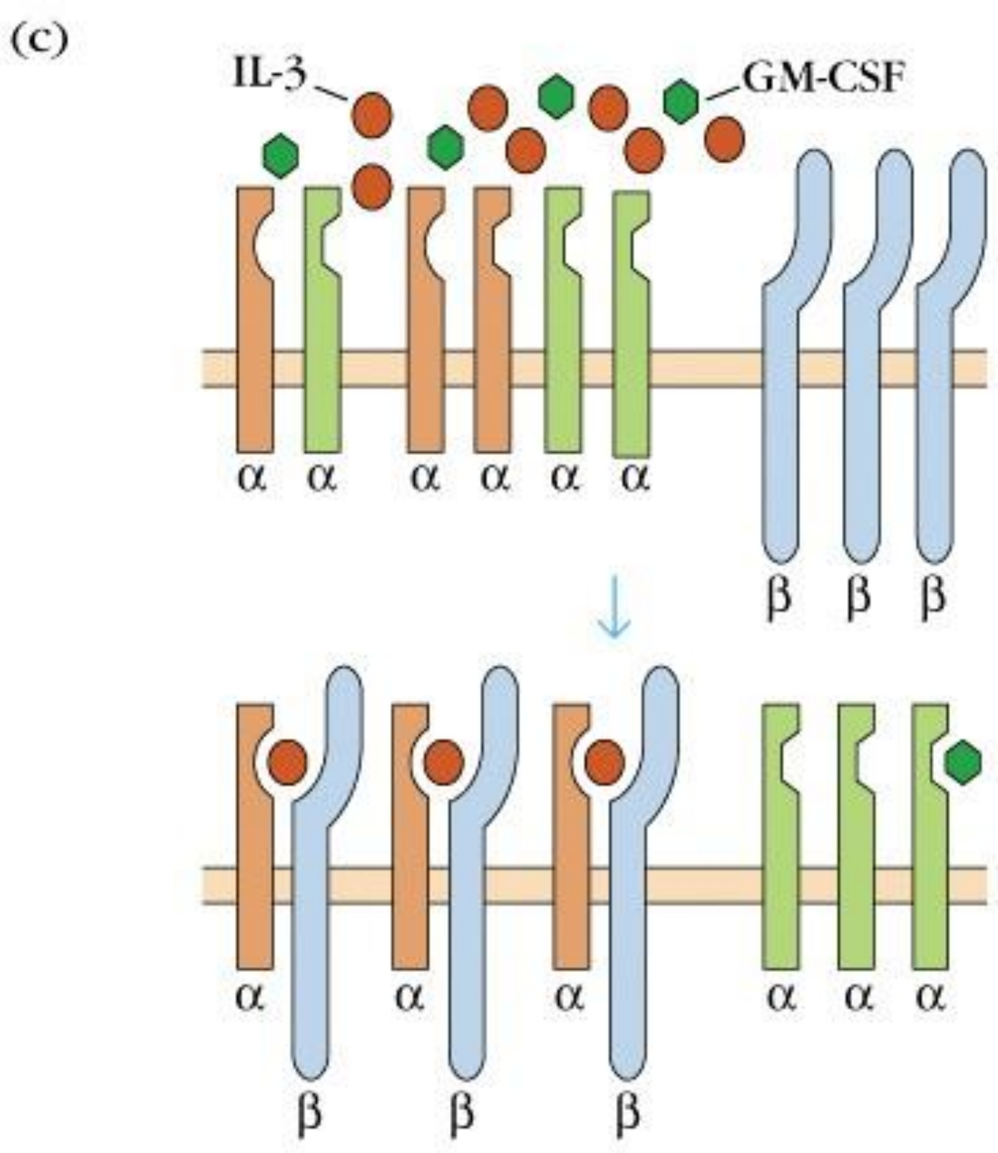


	Intermediate affinity IL-2R	High affinity IL-2R	Low affinity IL-2R
Subunit composition:	IL-2Rβ IL-2Rγ	IL-2Rα IL-2Rβ IL-2Rγ	IL-2Rα
Affinity constant (K_a):	$10^7 M$	$10^{11} M$	$10^8 M$
Dissociation constant (K_d):	$10^{-9} M$	$10^{-11} M$	$10^{-8} M$
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated CD4+ and CD8+ T cells Activated B cells (low numbers)	

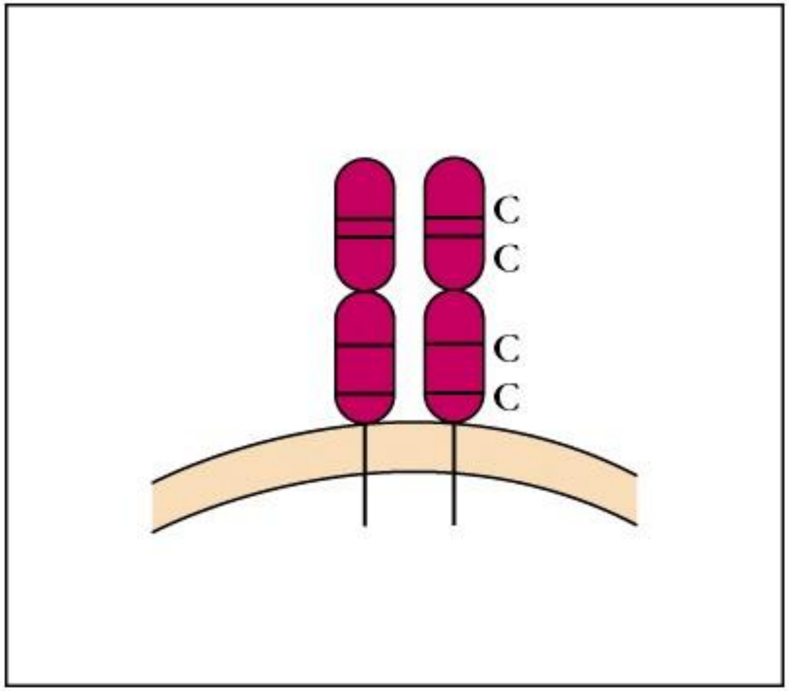
Interactions between Cytokine-specific Subunits and a Common Signal-transducing Subunit of Cytokine Receptors



Competition of Ligand-binding Chains of Different Receptors for a Common Subunit Can Produce **Antagonistic Effects** between Cytokines



(c) Class II cytokine receptors
(interferon)



IFN-α

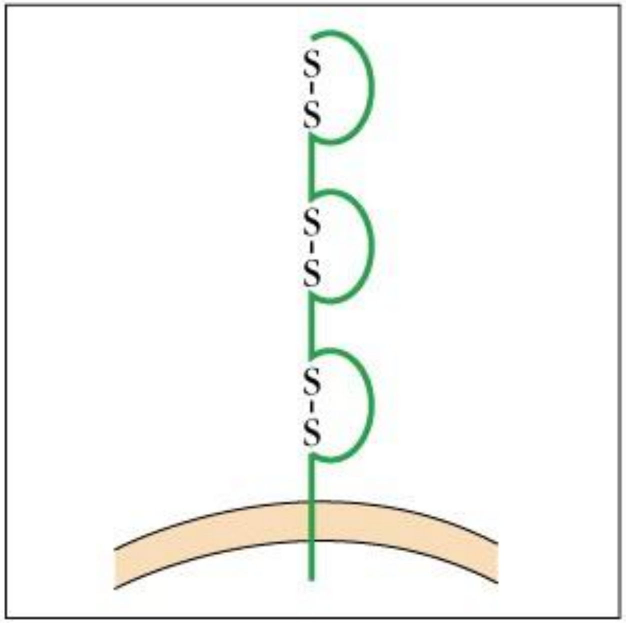
IFN-β

IFN-γ

IL-10

RECEPTOR FAMILY LIGANDS

(a) Immunoglobulin superfamily
receptors

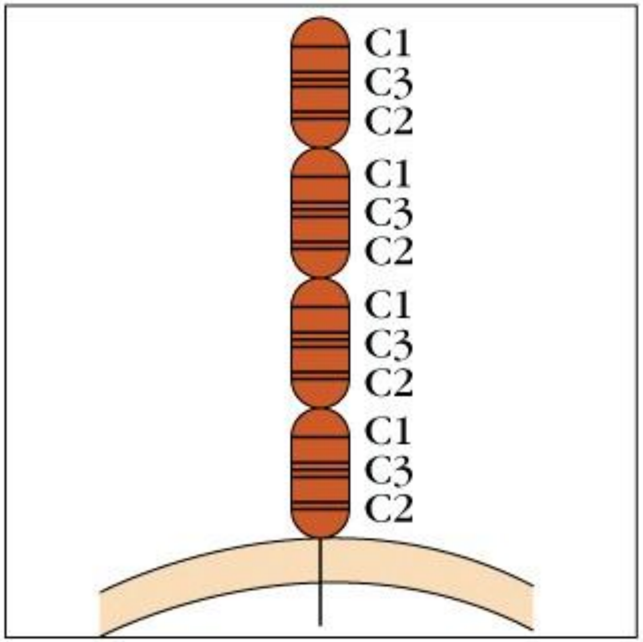


IL-1

M-CSF

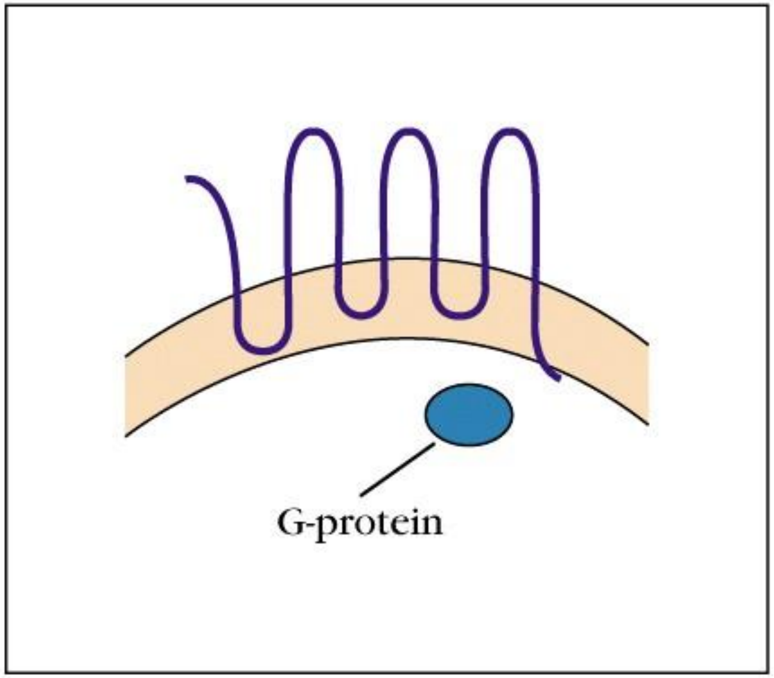
C-Kit

(d) TNF receptors



- TNF-α
- TNF-β
- CD40
- Nerve growth factor (NGF)
- FAS

(e) Chemokine receptors



- IL-8
- RANTES
- MIP-1
- PF4
- MCAF
- NAP-2

Signaling through cytokine receptor:

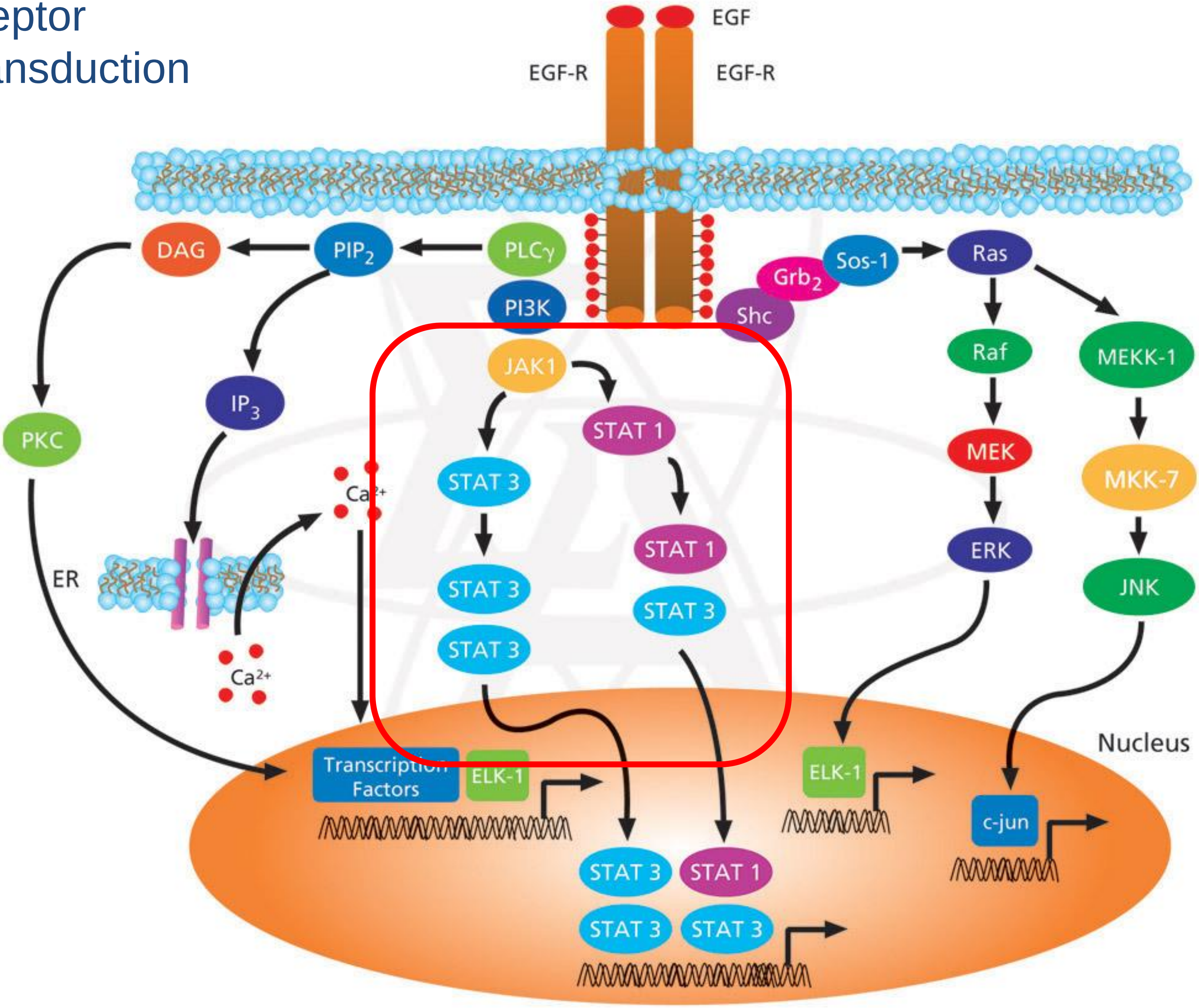
JAK-Stat Pathway

JAK: Janus kinases
Stat: signal tranducers and activators of transcription

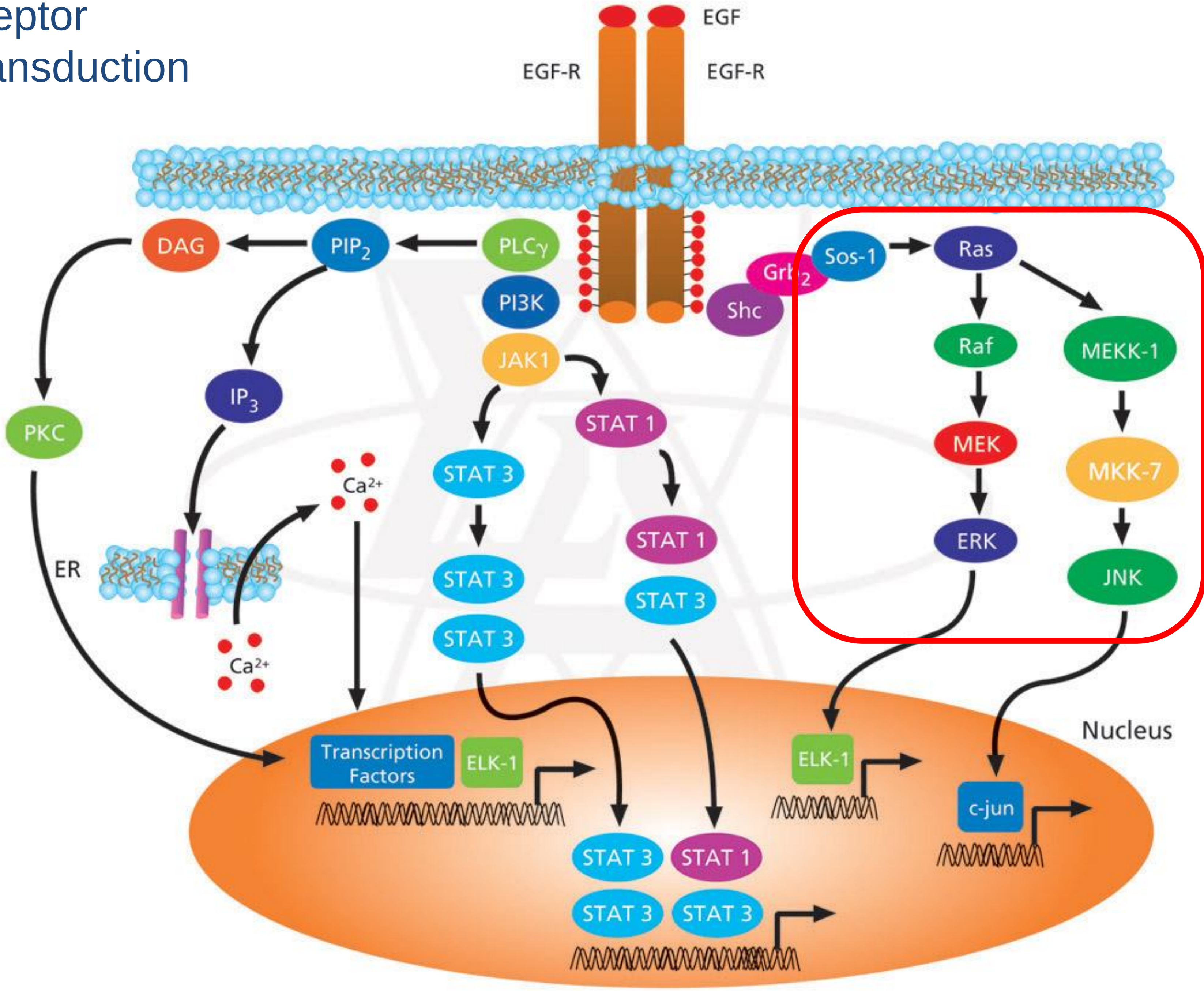
MAPK-pathway

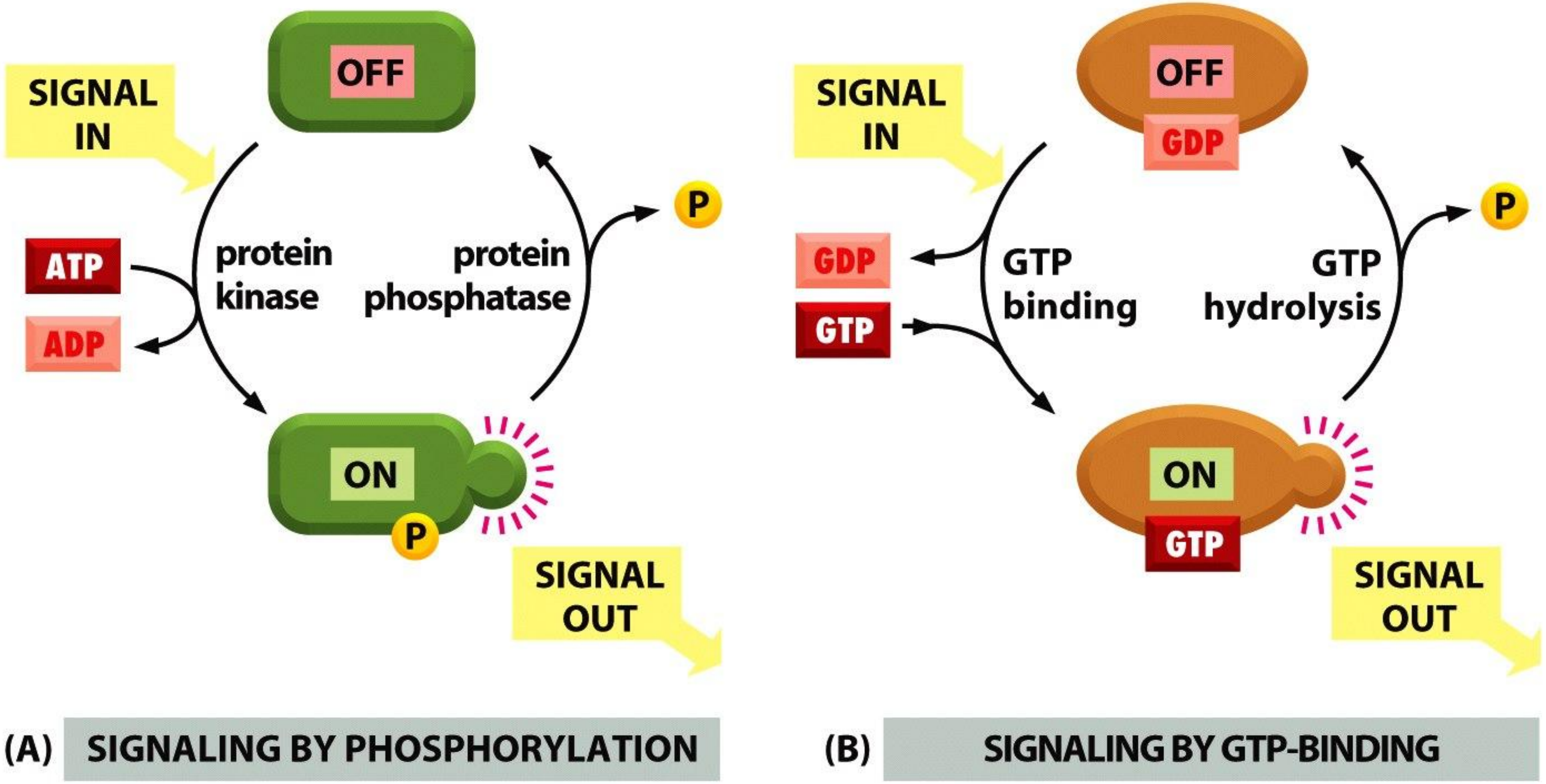
Rho=GTPases; MAPK –mitogen-activated kinases; c-Jun – transcription regulator

EGF Receptor Signal Transduction Pathway



EGF Receptor Signal Transduction Pathway





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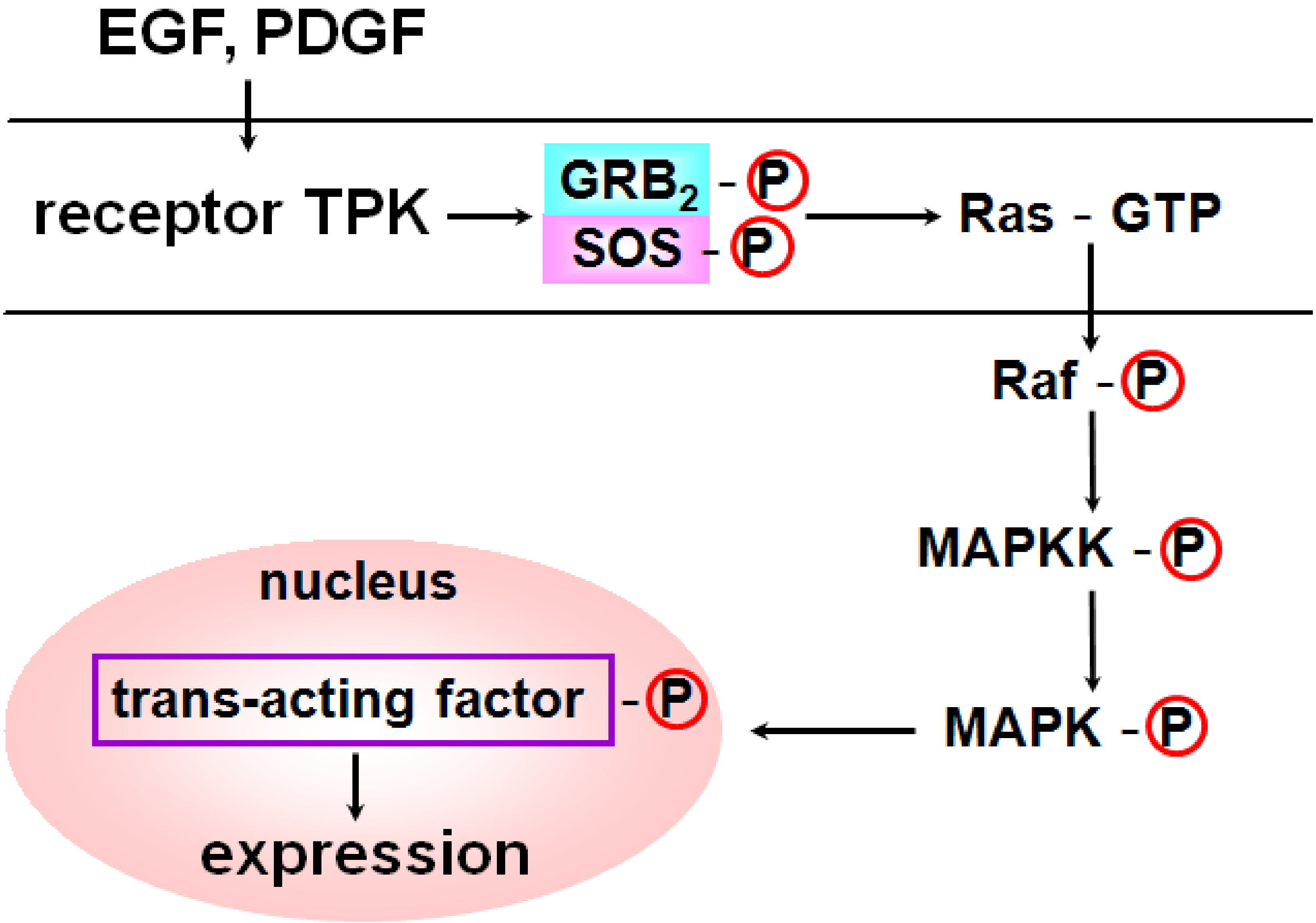
Two types of intracellular signaling proteins that act as molecular switches. In both cases, a signaling protein is activated by the addition of a phosphate group and inactivated by the removal of the phosphate. (A) The phosphate is added covalently to the signaling protein by a protein kinase. (B) A signaling protein is induced to exchange its bound GDP for GTP. To emphasize the similarity in the two mechanisms, ATP is shown as APPP, ADP as APP, GTP as GPPP, and GDP as GPP.



EGF, PDGF

receptor TPK

GRB$_2$ - Ⓟ

SOS - Ⓟ

Ras - GTP

Raf - Ⓟ

MAPKK - Ⓟ

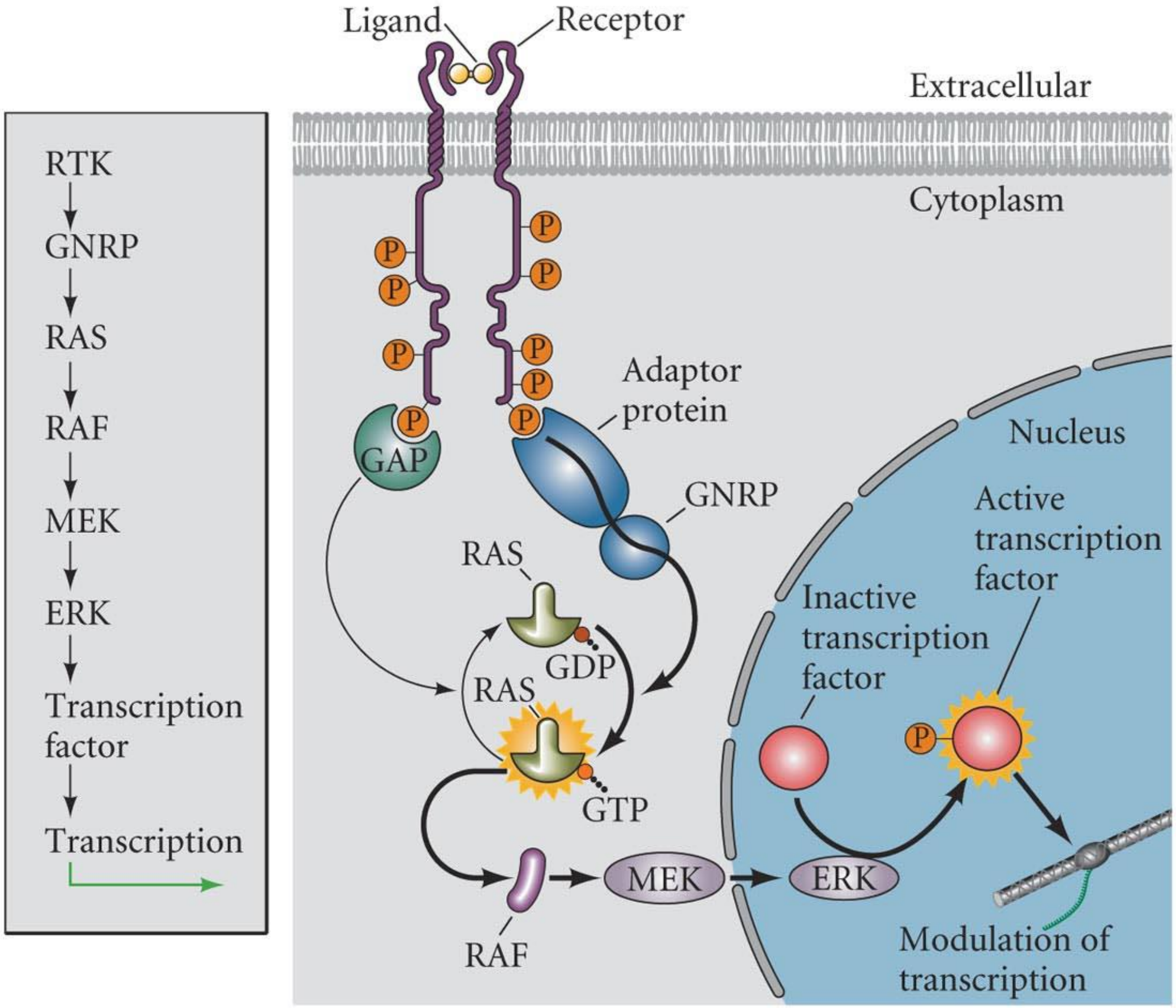
MAPK - Ⓟ

nucleus

trans-acting factor - Ⓟ

expression

RTK pathway



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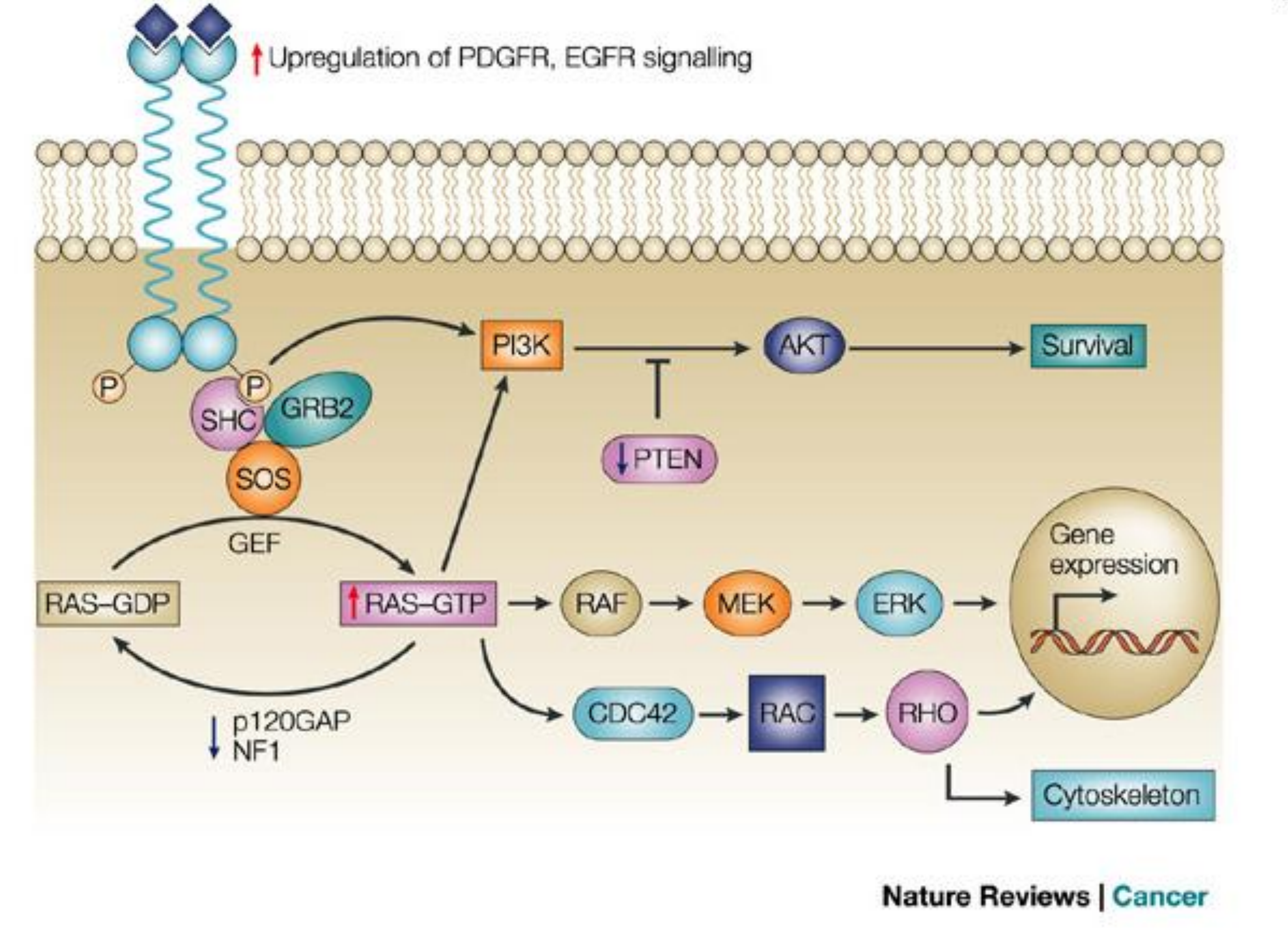
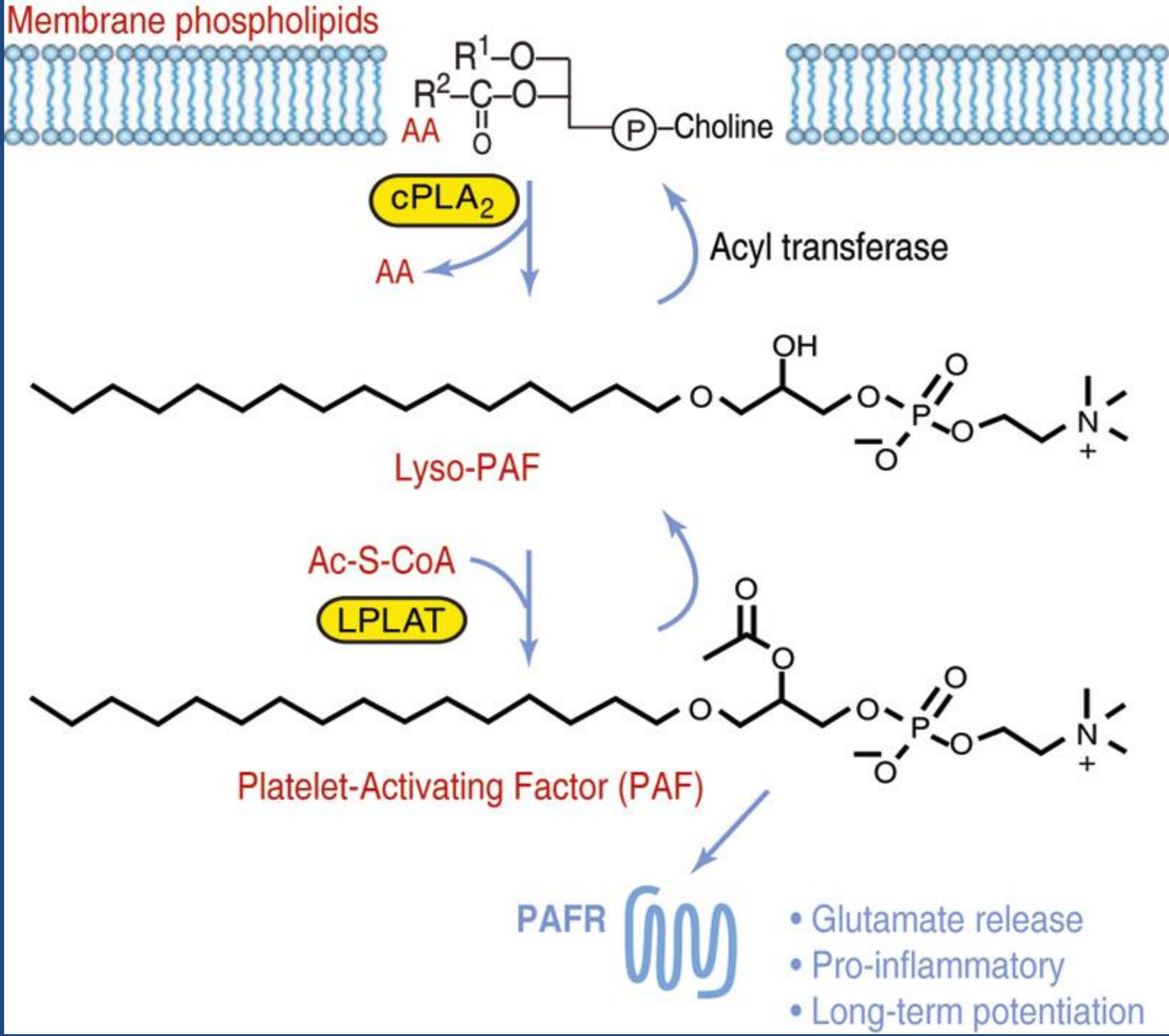
Transforming Growth Factor Receptor

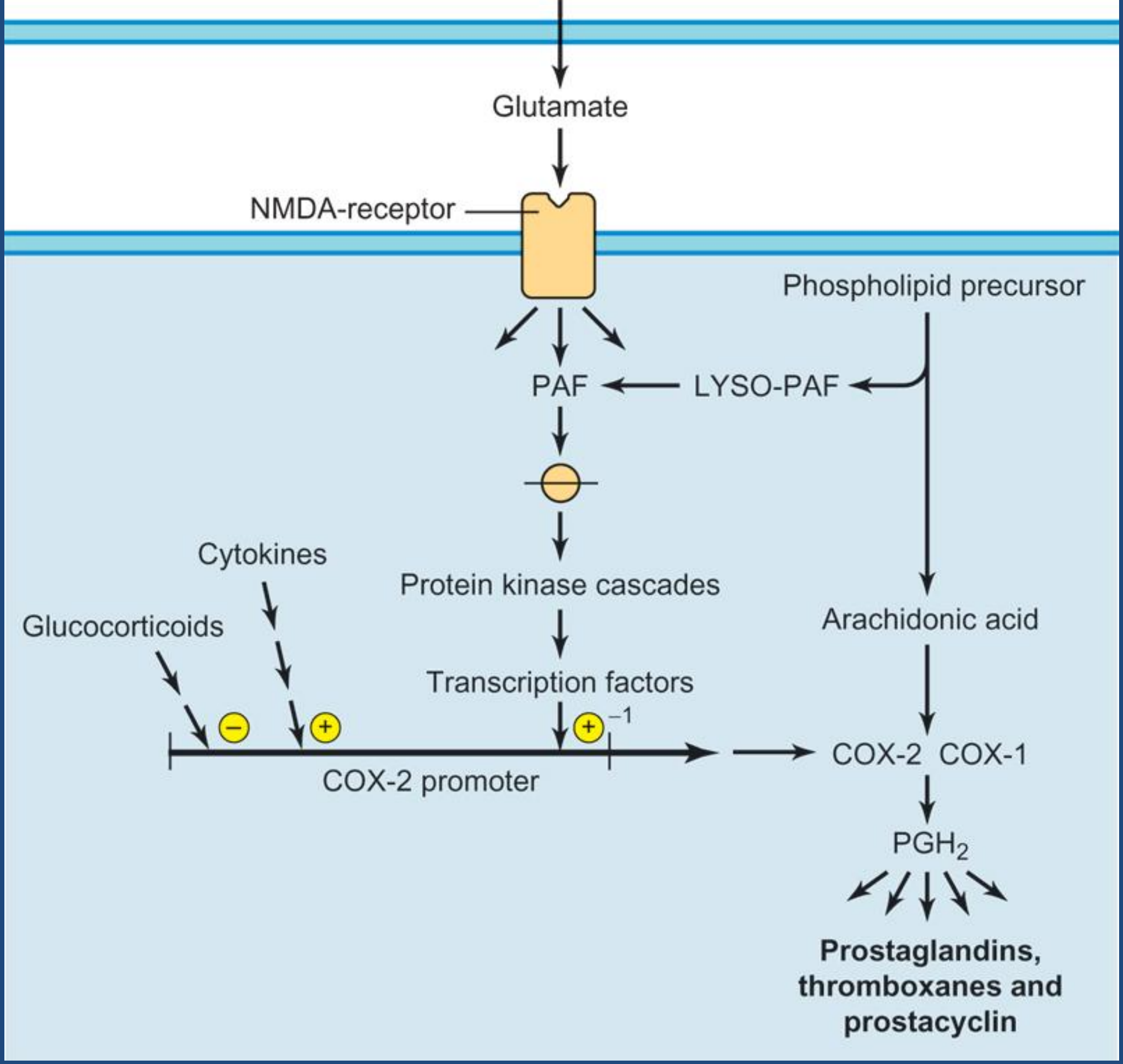


Other paracrine regulators

The platelet-activating factor (PAF) pathway



Activated cytosolic phospholipase A2 (cPLA2) catalyzes the cleavage of the arachidonoyl (AA) ester group at the 2-position of ether glycerophospholipids to form free arachidonic acid (AA) and lyso-PAF, which is rapidly re-incorporated into the phospholipid via an acyl transferase enzyme, or is acetylated by a lysophospholipid acyltransferase enzyme (LPLAT) to form PAF. Deactivation of PAF takes place via the acetyl group hydrolysis and re-acylation, followed by reuptake into the membrane phospholipids.



Signaling events linking synapse activation and cyclooxygenase-2 (COX-2) gene expression in neurons. *N* -methyl- D -aspartate (NMDA) receptor activation by glutamate leads to phospholipase A_2 (*PLA*$_2$) activation and the generation of platelet-activating factor (*PAF)* and of arachidonic acid. PAF activates COX-2 gene expression through protein kinase cascades and transcription factors. The COX-2 promoter is also a target for cytokines (activation) and glucocorticoids (inhibition). COX-2 protein then catalyzes the conversion of arachidonic acid into prostaglandin H2 (PGH2), the precursor of eicosanoids

Prostaglandin signaling pathway triggered by the excitatory amino acid neurotransmitter glutamate

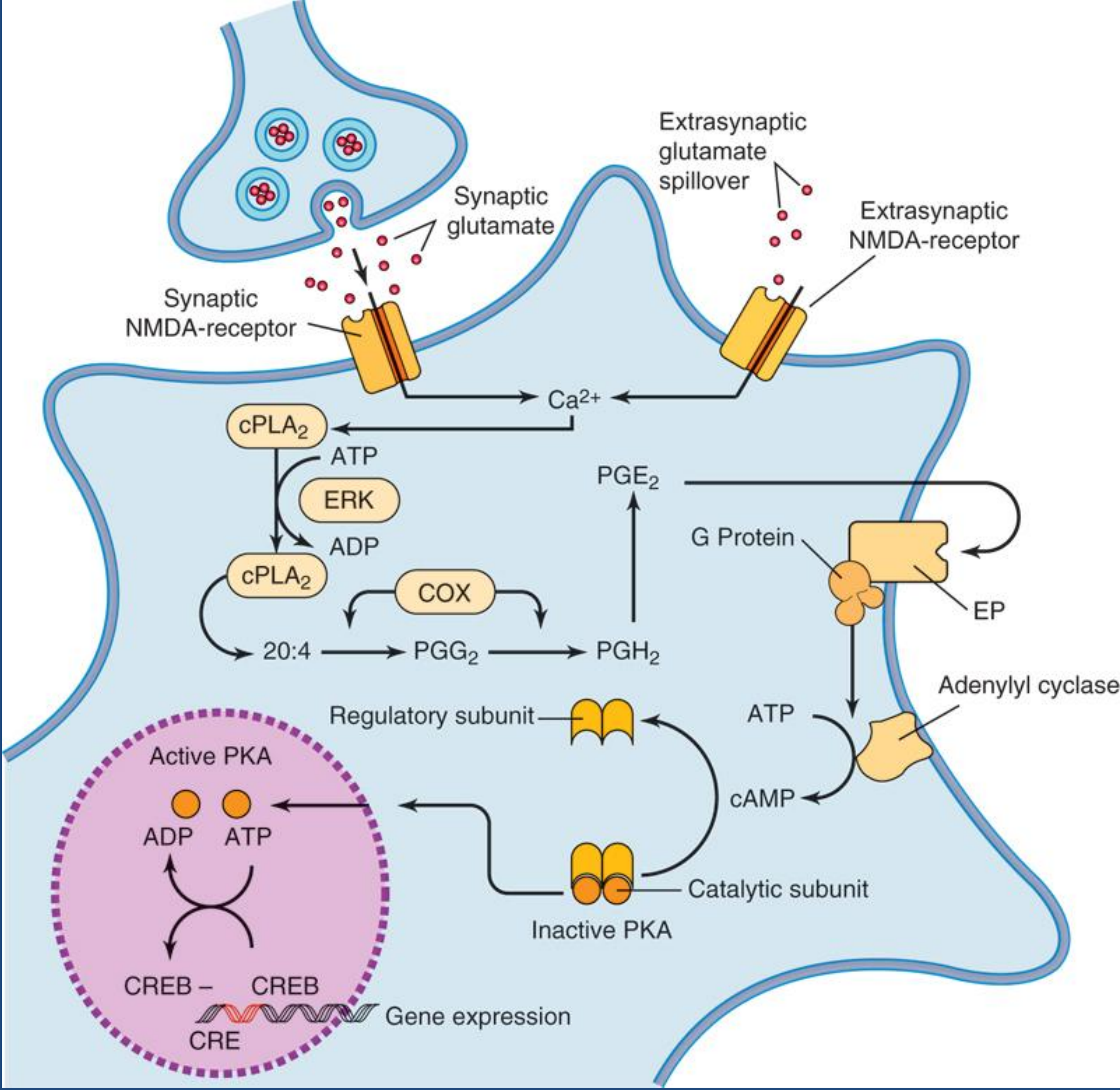
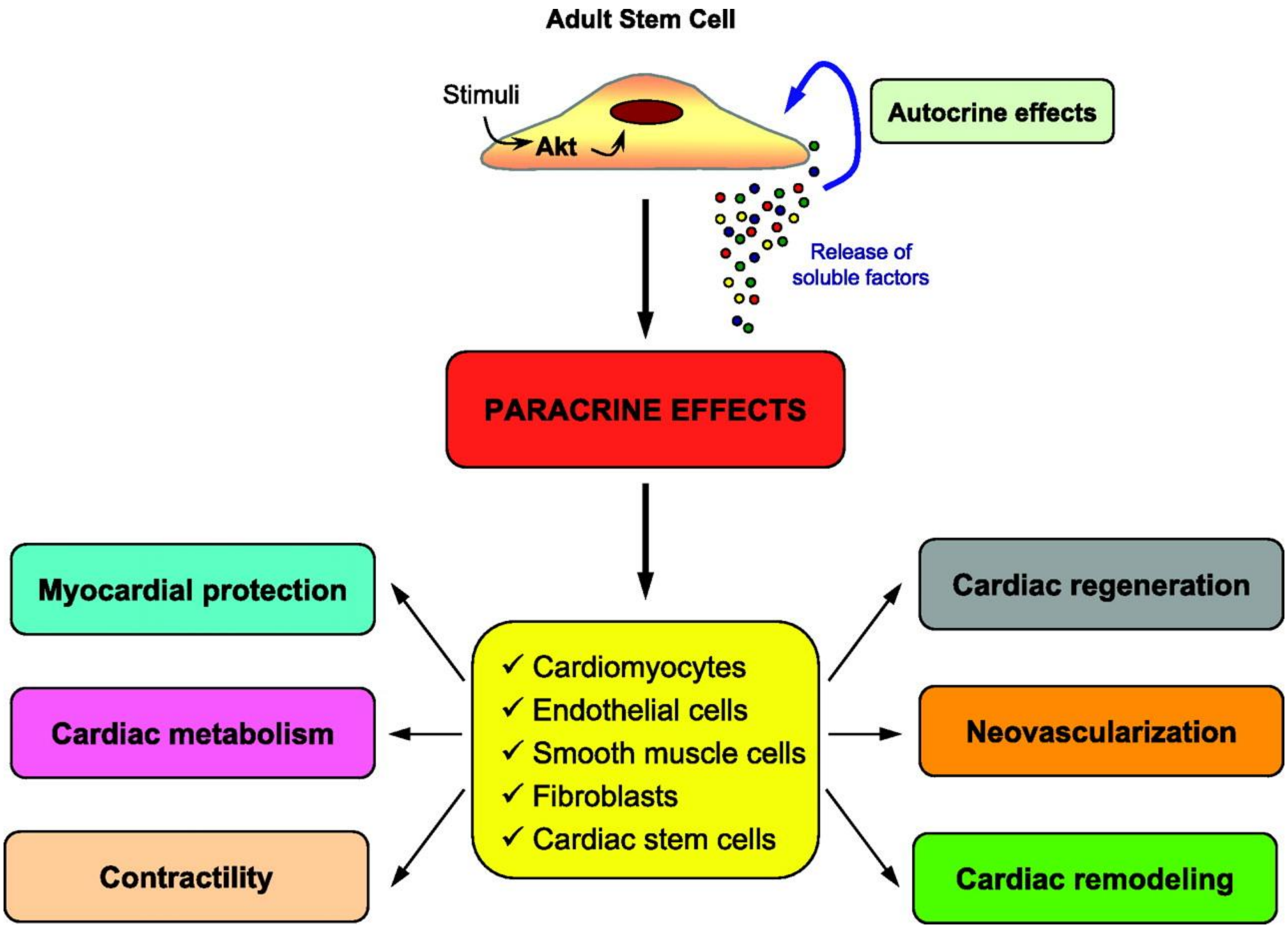


Figure 2. Paracrine/autocrine mechanisms in stem cell signaling and therapy.



Gnecchi M et al. Circulation Research. 2008;103:1204-1219

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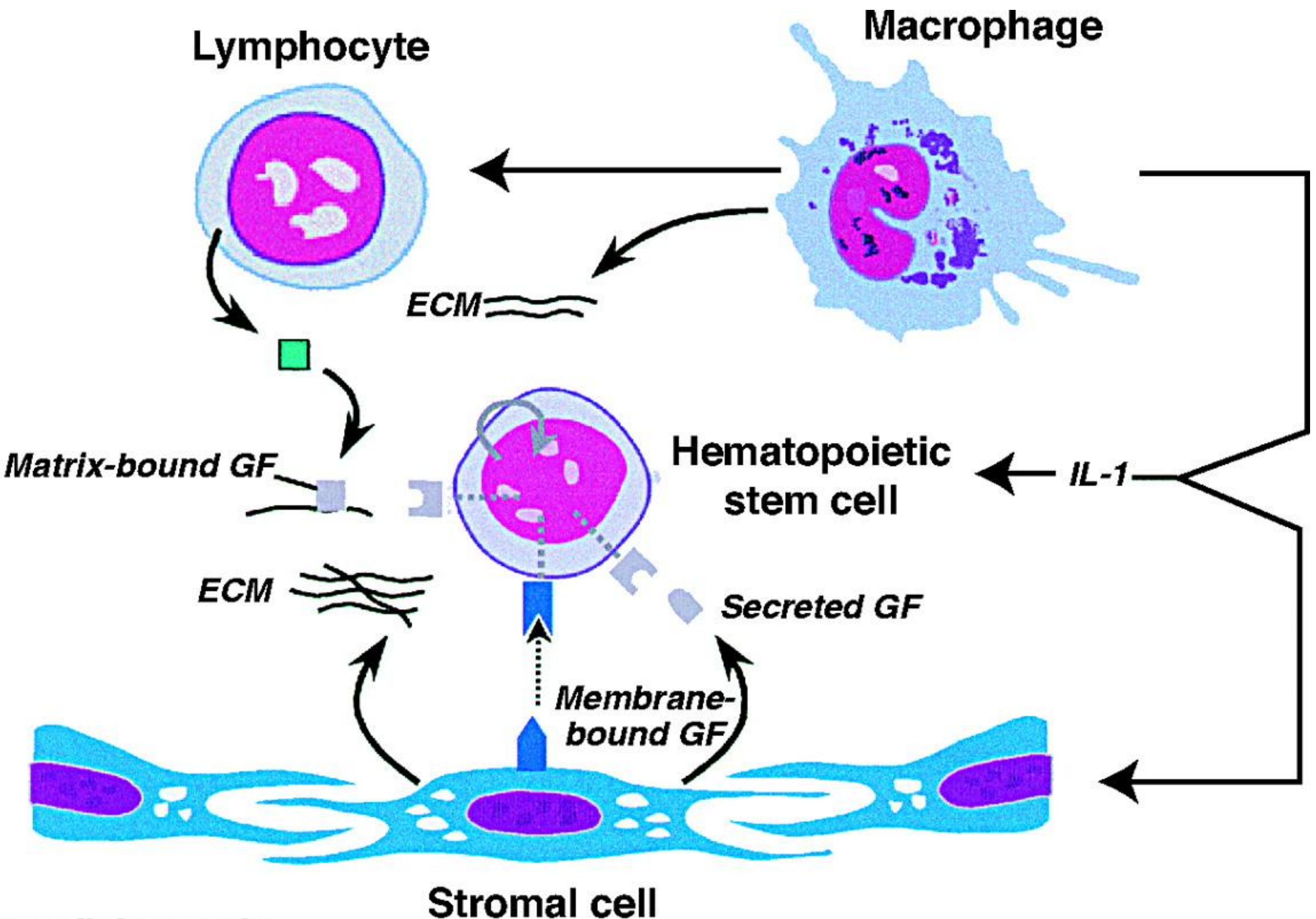
The hematopoietic microenvironment.



ECM = extracellular matrix
GF = growth factor
IL = interleukin

Gabrilove J L The Oncologist 2001;6:4-7

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